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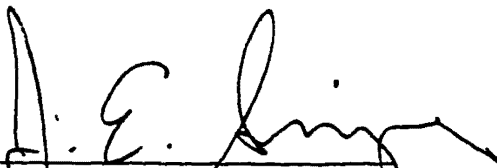4301 JONES BRIDGE ROAD
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Title of Thesis: "Effects of Nicotine and Nicotinic
Antagonists on the Acoustic Startle
Response and on Pre-Pulse Inhibition in
Rats"

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Master of Science
1996

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ABSTRACT

Title of Thesis: Effects of Nicotine and Nicotinic

Antagonists on the Acoustic Startle

Response and on Pre-Pulse Inhibition in

Rats

Eric Jon Popke, Master of Science, 1996

Thesis directed by: Neil E. Grunberg, Ph.D.

Professor

Department of Medical and Clinical

Psychology

In rats, nicotine has effects on the amplitude of the
acoustic startle response (ASR) and on pre-pulse inhibition
of the acoustic startle response (PPI) that are consistent
with an inverted U-shaped dose-effect. Because ASR and PPI
have been used to study processes that underlie attention
and sensory gating, these effects of nicotine in rats are
viewed as consistent with reports that nicotine can enhance
attention in human smokers. However, the mechanisms
underlying these effects of nicotine have not been
identified. The purpose of the present experiment was to
determine whether nicotine's effects on ASR and PPI are a
result of its effects in the central nervous system or if
nicotine's effects on ASR and PPI are due to its effects

peripherally. Acute subcutaneous (SC) administration of nicotine (0.01 mg/kg or 0.5 mg/kg nicotine), the centrally-active nicotinic antagonist mecamylamine (1.0 mg/kg), and/or the peripherally-active nicotinic antagonist hexamethonium (1.0 mg/kg)was used to evaluate the roles of peripheral and central nicotinic cholinergic receptors in mediating nicotine's effects on ASR and PPI in female Sprague-Dawley rats.

Nicotine, mecamylamine, and hexamethonium each enhanced PPI when administered with saline. Mecamylamine attenuated effects of 0.01 mg/kg nicotine on PPI but did not alter effects of 0.5 mg/kg nicotine. Hexamethonium had inconsistent effects on PPI when administered with 0.01 mg/kg nicotine or 0.5 mg/kg nicotine. Mecamylamine and hexamethonium enhanced PPI when administered together. Because nicotine, mecamylamine, and hexamethonium each increased PPI relative to saline, it is suggested that nicotine, mecamylamine, and hexamethonium may share a similar mechanism of action to affect PPI. Further, it is likely that ASR and PPI are influenced by peripheral as well as central nicotinic-cholinergic receptors. Nicotine did not alter ASR amplitudes when administered with saline or with either nicotinic antagonist. Nicotinic antagonists also did not alter ASR when administered without nicotine.

Effects of Nicotine and Nicotinic Antagonists on
the Acoustic Startle Response and on Pre-Pulse Inhibition
in Rats

by

Eric Jon Popke

Masters's Thesis submitted to the Faculty of the

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INTRODUCTION

The acoustic startle paradigm can be used with rats to study nicotine's effects on processes that underlie sensory gating (Swerdlow, Braff, Geyer, & Koob, 1986) and attention (Acri, Morse, & Grunberg, 1991; Acri, Morse, Popke, & Grunberg, 1994; Grunberg, Acri, & Popke, 1994). Reports suggest that nicotine may enhance the amplitude of the acoustic startle response (ASR) and increase pre-pulse inhibition of ASR (PPI) in male (Acri, 1994; Popke, Acri, & Grunberg, 1994) and in female rats (Acri, et al., 1994; Popke, et al., 1994). Because ASR and PPI have been interpreted as indices of sensory gating (Acri, 1994; Acri, et al., 1994; Swerdlow, Braff, Geyer, & Koob, 1986; Swerdlow, Caine, Braff, & Geyer, 1992), effects of nicotine to increase ASR and PPI may be consistent with reports that nicotine enhances attention in smokers (Wesnes & Warburton, 1983; Wesnes, Warburton, & Katz, 1983), nonsmokers (Provost & Woodward, 1991; Wesnes & Revell, 1984; Wesnes & Warburton, 1984), and patients with Alzheimer's disease (Sahakian, Jones, Levy, & Gray, 1989; Jones, Sahakian, Levy Warburton, & Gray, 1992). The mechanisms that underlie nicotine's effects on ASR and PPI, however, have not been established. Because nicotine and nicotinic drugs may have value in the prevention and treatment of specific diseases (Sahakian, et al., 1989; Jarvik, 1991; Jones et al., 1992), it would be valuable to know the mechanism by which nicotine affects ASR

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and PPI. One possibility is that nicotine-induced changes in ASR and PPI are directly mediated by a nicotinic cholinergic mechanism. If this is true, then it is important to determine the nature and site of this mechanism.

The present experiment was designed to evaluate the roles of central and peripheral nicotinic cholinergic receptors in mediating effects of nicotine on ASR and PPI. To accomplish this purpose, rats received a peripheral subcutaneous (SC) injection of either mecamylamine, a nicotinic cholinergic antagonist that readily crosses the blood-brain barrier, or hexamethonium, a nicotinic cholinergic antagonist that does not cross the blood-brain barrier at the doses used presently, prior to nicotine administration and acoustic startle testing. The effects of nicotine on ASR and PPI after administration of these two antagonists may help to elucidate the site of nicotine's actions on processes that underlie sensory gating.

The Acoustic Startle Response

The acoustic startle response (ASR) is a simple behavior that occurs in response to abrupt sensory stimuli. The neural circuitry that underlies this response is thought to include the auditory nerve, the ventral cochlear nucleus, nuclei of the lateral lemniscus, nucleus reticularis pontis caudalis, spinal neuron, and lower motor neuron (Davis, Gendelman, Tischler, & Gendelman, 1982). For several

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reasons, this behavior provides an excellent animal model to study effects of drugs on behavior. First, the acoustic startle response can be elicited using identical stimulus parameters in humans and in animals, thereby enabling cross-species generalizations to be made (Swerdlow, Caine, Braff, & Geyer, 1992). Second, although the primary neural circuitry that underlies the acoustic startle response involves structures at, or below, the midbrain, the response exhibits several types of plasticity that are thought to involve "higher" brain structures (Swerdlow, et al., 1992). One such form of plasticity is known as pre-pulse inhibition (PPI) and will be discussed in detail in subsequent sections.

Numerous studies have reported effects of drugs to alter the amplitude of ASR. ASR is increased by dopaminergic agents such as apomorphine (Davis, 1988), d-amphetamine (Davis, Svensson, Aghajanian, 1975; Kokkinidis & Anisman, 1978), and cocaine (Harty & Davis, 1985), and is inhibited by ethanol (Pohorecky, Cagan, Brick, & Jaffe, 1976). Recently, studies have examined effects of nicotine on ASR (Acri, et al., 1991; Acri, et al., 1994; Popke, et al., 1994).

Nicotine and ASR.

Several studies have examined effects of nicotine on the amplitude of the acoustic startle response. Acri, et al. (1991) reported effects of chronic nicotine (12

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mg/kg/day; administered by osmotic minipump) to increase ASR amplitude relative to saline controls. Others have reported similar effects of acute nicotine (0.01 mg/kg nicotine; SC) to increase ASR amplitudes relative to controls (Acri, et al., 1994; Popke, et al., 1994). These results have been interpreted as reflecting changes attentional processes produced by nicotine (Acri, et al., 1994). However, these results fail to identify nicotine's site of action to affect ASR. It is possible that nicotine affects ASR via central nicotinic-cholinergic receptors. Alternatively, nicotine may affect ASR via peripheral nicotinic-cholinergic receptors.

Pre-Pulse Inhibition of Acoustic Startle

Pre-pulse inhibition (PPI) refers to the reduction in startle amplitude that occurs when the startling stimulus is briefly preceded by a non-startling tone. As is the case for ASR, PPI occurs in humans and in animals, making cross-species generalizations possible. PPI is not thought to reflect conditioning for several reasons. First, PPI occurs on the first exposure to the tone and is not sensitive to habituation or extinction. Further, the interval between the presentation of the pre-pulse and the presentation of the startle stimulus is too short to permit volitional processing. Therefore, it appears that the phenomenon of pre-pulse inhibition reflects an innate "gating" mechanism relating to sensory-motor function (Swerdlow, et al., 1992).

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This supposition has led to the use of the pre-pulse inhibition paradigm to study attentional processes (Acri, et al., 1994) and to model the time-dependent sensory gating deficits associated with schizophrenia (Swerdlow, et al., 1986).

The neural circuitry that underlies PPI is thought to include hippocampal efferents to the striatum and striatal GABAergic efferents to the ventral pallidum (Swerdlow, et al., 1992). Pallidal efferents may impinge on the primary acoustic startle circuit at the level of the mesencephelon. Additional modulation of PPI occurs in the striatum and is thought to involve primarily D_2 receptors (Swerdlow et al. 1992).

<u>Nicotine and PPI</u>

Studies of nicotine's effects on PPI have yielded results that are consistent with nicotine's enhancing effects on attention. Specifically, it has been reported that acute (0.01 mg/kg; SC) (Acri, et al, 1994; Popke, et al., 1994) and chronic (12 mg/kg/day; administered by osmotic minipump)(Acri, 1994) nicotine each enhance pre-pulse inhibition relative to controls; Nicotine administration increases the extent to which the startle response is reduced when the startling stimulus is preceded by a non-startling tone. As noted for ASR, reports that systemic nicotine increased PPI cannot identify the site at which nicotine acts to produce these effects. It is likely

that nicotine affects PPI via central nicotinic-cholinergic receptors because PPI involves higher-order processes. However, because nicotine has effects in the periphery as well as in the central nervous system, it is possible that nicotine may affect PPI by influencing peripheral nicotinic-cholinergic receptors either at autonomic ganglia or neuromuscular junctions. These peripheral influences may manifest as changes in the startle response.

The present experiment used a centrally-active nicotinic-cholinergic antagonist (mecamylamine) or a centrally-inactive nicotinic-cholinergic antagonist (hexamethonium) to selectively block nicotinic receptors prior to nicotine administration and ASR and PPI testing. If nicotine's effects on ASR and PPI are altered by mecamylamine, but not by hexamethonium, then results would suggest that a central nicotinic mechanism may mediate nicotine's effects on ASR and PPI. If nicotine's effects on ASR and PPI are altered by hexamethonium as well as by mecamylamine, then results would suggest that peripheral mechanisms may also mediate nicotine's effects on ASR and PPI.

OVERVIEW

The present experiment examined effects of nicotine, mecamylamine, and hexamethonium on the acoustic startle response (ASR) and on pre-pulse inhibition (PPI) in female rats. Although male and female rats are each sensitive to nicotine, published reports indicate that female rats may be somewhat more sensitive to some effects of nicotine than are males (Grunberg, Winders, & Popp, 1987; Stone, Dembroski, Costa, & MacDougall, 1991). Therefore, only female rats were used for the present study of nicotine and nicotinic antagonists. Based on previous reports (Acri, et al., 1994; Popke, et al., 1994), it was hypothesized that acute administration of 0.01 mg/kg nicotine would enhance ASR and PPI and that acute administration of 0.5 mg/kg nicotine would produce levels of ASR and PPI that were indistinguishable from controls. Because the mechanisms that underlie ASR and PPI are likely to be centrally located (Davis, et al., 1982; Swerdlow, et al., 1992), it was hypothesized acute administration of the centrally-active nicotinic antagonist, mecamylamine would alter nicotine's effects in a way that is consistent with a leftward shift of nicotine's inverted U-shaped dose-response curve. More specifically, it was hypothesized that mecamylamine pretreatment would render effects of 0.01 mg/kg nicotine that were indistinguishable from controls and would render effects of 0.5 mg/kg nicotine that resembled effects of 0.01

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mg/kg nicotine administered without mecamylamine. Hexamethonium, on the other hand, which does not cross the blood-brain barrier and therefore does not block central nicotinic receptors, should not alter effects of either dose of nicotine on ASR or on PPI. Finally, it was hypothesized that neither mecamylamine nor hexamethonium would alter ASR or PPI when administered without nicotine.

Subjects received three exposures to the experimental procedure. During the first exposure, subjects were tested without receiving injections. The purpose of this exposure was to habituate subjects to the testing apparatus and procedures. During the second exposure, subjects were tested after receiving two injections of saline. The purpose of this baseline exposure was to habituate subjects to the potentially stressful injection procedure. During the third exposure, subjects were tested after receiving one of the 10 dosing regimens outlined in Table 1. The amplitude of the acoustic startle response (ASR) was measured by an interface microcomputer as the maximum response occurring within 200 ms of the onset of the startle-eliciting stimulus. PPI was determined by subtracting the response to trials preceded by a pre-pulse from the response to similar trials presented without pre-pulse. The amount of pre-pulse inhibition was divided by the responses to similar trials presented without pre-pulse to determine the percentage of the response inhibited.

HYPOTHESES

Hypothesis 1. It was hypothesized that subjects would exhibit greater startle response amplitudes in response to the 122 dB stimuli than in response to the 112 dB stimuli.

Rationale. Published reports indicate a positive linear relationship between intensity of the startling stimulus and the magnitude of the acoustic startle response (Acri 1994; Acri, et al., 1994)

Hypothesis 2. It was hypothesized that acute administration of 0.01 mg/kg nicotine would increase ASR and PPI relative to controls.

Rationale. Previous reports indicate that acute administration of 0.01 mg/kg nicotine increases ASR (Popke, et al., 1994) and PPI (Acri, et al., 1994; Popke, et al., 1994) in rats. Therefore, acute administration of 0.01 mg/kg nicotine should increase ASR and PPI relative to controls.

Hypothesis 3. It was hypothesized that acute administration of 0.5 mg/kg nicotine would produce levels of ASR and PPI that are indistinguishable from controls.

Rationale. Previous reports indicate that nicotine has an inverted U-shaped dose-effect on ASR and on PPI (Acri, et al., 1994). Effects of 0.5 mg/kg nicotine on ASR and PPI are thought to reflect the descending limb of this inverted U-shaped curve and have been shown to be indistinguishable from controls (Acri, et al., 1994). Therefore, acute

administration of 0.5 mg/kg nicotine should produce levels of ASR and PPI that resemble controls. Administration of this dose of nicotine will allow detection of the hypothesized shift of nicotine's dose-response curve by mecamylamine.

Hypothesis 4. It was hypothesized that acute administration of 1.0 mg/kg mecamylamine would antagonize effects of nicotine on ASR and PPI and would result in a leftward shift in the dose-effect of nicotine. Such a shift should result in effects of 0.01 mg/kg nicotine that are indistinguishable from saline controls.

Rationale. Previous reports indicate that mecamylamine can antagonize behavioral effects of nicotine which, like ASR and PPI, are believed to be centrally mediated (Nakamura, Goshima, Yue, Miyame, & Misu, 1993). Therefore, enhancing effects of 0.01 mg/kg nicotine should be antagonized by administration of mecamylamine. This antagonizing effect of mecamylamine should be manifest as a leftward shift in the dose-effect of nicotine on ASR and PPI. In other words, in the presence of mecamylamine, effects of 0.01 mg/kg nicotine should be indistinguishable from controls.

Hypothesis 5. It was hypothesized that acute administration of 1.0 mg/kg mecamylamine would antagonize effects of nicotine and would result in a leftward shift in the dose-effect of nicotine. Such a shift should result in

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effects of 0.5 mg/kg nicotine that are similar to effects of 0.01 mg/kg nicotine administered without mecamylamine.

Rationale. Previous reports indicate that mecamylamine can antagonize behavioral effects of nicotine which, like ASR and PPI, are believed to be centrally mediated (Nakamura, et al., 1993). Therefore, effects of 0.5 mg/kg nicotine should be antagonized by administration of mecamylamine. This antagonizing effect of mecamylamine should be manifest as a leftward shift in the dose-effect of nicotine on ASR and PPI. In other words, in the presence of mecamylamine, effects of 0.5 mg/kg nicotine should resemble effects of 0.01 mg/kg nicotine administered without mecamylamine.

Hypothesis 6. It was hypothesized that enhancing effects of nicotine on ASR and PPI would be unaltered by administration of 1.0 mg/kg hexamethonium.

Rationale. ASR and PPI are believed to be mediated by central nervous system structures including the auditory nerve, the ventral cochlear nucleus, nuclei of the lateral lemniscus, nucleus reticularis pontis caudalis, hippocampus, and striatum (Davis, et al., 1982; Swerdlow, et al, 1992). Because hexamethonium does not cross the blood-brain barrier at doses administered presently, it should not antagonize effects of nicotine at these central nervous system sites. Therefore, effects of nicotine on ASR and PPI should be unaltered by hexamethonium.

Hypothesis 7. It was hypothesized that neither mecamylamine nor hexamethonium would alter ASR or PPI when administered without nicotine.

Rationale. Previous reports indicate that neither mecamylamine (Danobar, Depaulis, Marescaux, & Vergnes, 1993; Moran, 1993) nor hexamethonium (Faiman, Deerausquin, & Baratti, 1992) alter centrally-mediated behaviors at the doses used presently. Therefore, neither hexamethonium nor mecamylamine should alter ASR or PPI when administered without nicotine.

METHOD

Subjects.

Subjects were 90 female Sprague-Dawley rats (Charles River Laboratories, Willmington, MA) weighing 250 g and all roughly 10 weeks old at the beginning of the experiment. Although male and female rats are each sensitive to nicotine, published reports indicate that female rats may be somewhat more sensitive to some effects of nicotine than are males (Grunberg, et al. 1987; Stone, et al., 1991). Therefore, only female rats were used for the present study of nicotine and nicotinic antagonists. Animals were housed individually in 35.6 cm x 15.2 cm x 20.3 cm plastic cages with absorbent Pine-Dri, wood-chip bedding. Animals were maintained under a 12 h light/dark cycle (lights on at 0700) at approximately 23 degrees C and 50% relative humidity. Water and laboratory chow (Agway Prolab 3000) were available continuously.

Drugs and Drug Administration.

Nicotine. Nicotine solutions were prepared from nicotine dihydrochloride in concentrations of 0.01 mg nicotine base/ml 0.9% NaCl solution for the 0.01 mg/kg dosage, and 0.5 mg nicotine base/ml 0.9% NaCl solution for the 0.5 mg/kg dosage. These dosages were selected and prepared based on previous reports (Acri, et al., 1994; Popke, et al., 1994) and are believed to reflect critical points on an inverted U-shaped dose-effect of nicotine on

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PPI (Acri et al., 1994). Nicotine solutions were
administered SC (between the scapulae) using 1.0 ml syringes
with 22 gauge needles.

Mecamylamine. Mecamylamine solutions were prepared from
mecamylamine chloride (Research Biomedicals International,
Natick, MA)in a concentration of 1.0 mg mecamylamine base/ml
0.9% NaCl solution. The 1.0 mg/kg dosage was selected based
on published reports (Curzon, et al., 1994) and on pilot
data. Mecamylamine solutions were administered SC (between
the scapulae) using 1.0 ml syringes with 22 gauge needles.

Hexamethonium. Hexamethonium solutions were prepared
from hexamethonium hydrochloride (Sigma Chemical Company, St
Louis, MO) in a concentration of 1.0 mg hexamethonium
base/ml 0.9% NaCl solution. The 1.0 mg dosage was based on
published reports (Faiman, et al. 1991) and on pilot data.
Hexamethonium solutions were administered SC (between the
scapulae) using 1.0 ml syringes with 22 gauge needles.

Drug Administration. To determine whether nicotine's
effects on PPI would be affected by nicotinic antagonists,
animals received either nicotine or saline following
mecamylamine or hexamethonium treatment. Other animals
received either mecamylamine or hexamethonium alone, or
mecamylamine and hexamethonium together, to determine
effects of these nicotinic-cholinergic antagonists on PPI in
the absence of nicotine. The specific treatments presented
were: (1) saline followed by saline; (2) saline followed by

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0.01 mg/kg nicotine; (3) saline followed by 0.5 mg/kg nicotine; (4) mecamylamine followed by saline; (5) mecamylamine followed by 0.01 mg/kg nicotine; (6) mecamylamine followed by 0.5 mg/kg nicotine; (7) hexamethonium followed by saline; (8) hexamethonium followed by 0.01 mg/kg nicotine; (9) hexamethonium followed by 0.5 mg/kg nicotine; or (10) hexamethonium followed by mecamylamine. The second injection (saline, nicotine, or mecamylamine) was administered 20 minutes after the first injection (saline, mecamylamine, or hexamethonium). PPI was evaluated 15 minutes after the second injection. The time between the first injection and the end of acoustic startle testing was approximately 50 minutes in all treatment conditions.

Startle and Pre-Pulse Testing.

Acoustic startle was tested using a four-station acoustic startle system (Coulbourn Instruments, Allentown, PA) based on the procedures of Acri, et al. (1991). Specifically, animals were enclosed in 8 x 8 x 16 cm open air cages that restrict locomotion but do not restrain the animal. Cages were placed on one of four platforms in a sound attenuating test chamber. Background noise within the sound-attenuating startle chamber was produced by a ventilating fan and was measured at 56 dB. Startle-eliciting acoustic stimuli consisted of 20 ms noise bursts of 112 dB SPL or 122 dB SPL. Each stimulus had a 2 ms rise and decay

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time such that onset and offset were abrupt, a primary criterion for startle. Pre-pulse stimuli consisted of a 20 ms, 1 KHz pure tone of 68 dB SPL (12 dB above background). The intensity of this pre-pulse is comparable to those used by Curzon, et al. (1994). The onset of the pre-pulse stimuli preceded the onset of the startle-eliciting stimuli by 100 msec in all conditions. Trials with no stimuli and trials with pre-pulse alone also were presented. Each test session included eight presentations of each stimulus intensity both with and without pre-pulse. The order of presentation was randomized within blocks to ensure that each stimulus type was presented within seven trials of its last presentation and that none of the stimuli occurred more than once in sequence. Inter-trial intervals ranged randomly from 10 - 30 seconds. Each subject's movement in response to each stimulus was measured as voltage change by a strain gauge inside of the acoustic startle platform and was converted to grams of body weight change following analog to digital conversion. Responses were recorded by an interfaced computer as the maximum response occurring within 200 msec of the onset of the startle-eliciting stimuli.

Procedure.

Animals were gentled by daily handling for three days before the start of the experiment. Baseline testing consisted of one test session with no treatment and a second test session in which the animals received two injections of

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physiologic saline (0.9% NaCl). The purpose of the first baseline session was to acclimate subjects to the startle procedure to reduce the likelihood that the stress of a novel environment contributed to experimental effects observed during treatment. Data from this first baseline session were not included in subsequent statistical analyses. During the second baseline session, each animal received two injections of physiologic saline. The purpose of this second baseline session was to familiarize the animals with the injection procedure thereby further minimizing stress effects on PPI during subsequent drug treatments. In addition, responses to this second baseline day were used to assign subjects to conditions to ensure comparable pre-treatment responses. Test sessions for each animal were separated by at least four days to minimize effects of habituation on PPI (Thompson & Spencer, 1966).

Four days after the second baseline session, subjects were treated once using one of the ten dosing regimens outlined above. The second injection (saline, nicotine, or mecamylamine) was administered 20 minutes after the first injection (saline, mecamylamine, or hexamethonium). PPI was evaluated 15 minutes after the second injection. The time between the first injection and the end of acoustic startle testing was approximately 50 minutes in all treatment conditions. All manipulations were conducted between 1600-

1900 to maintain consistency with respect to the animals' circadian activity cycle.

Treatment of Data and Statistical Analysis.

Startle amplitudes were determined for each animal by subtracting the response to the no-stimulus control trials from the average peak response recorded during each of the other trial types. The amount of pre-pulse inhibition was determined by subtracting the response to the pre-pulse trials from the response to the trials in which the same stimulus was presented without pre-pulse. The amount of pre-pulse inhibition was divided by the response amplitude from trials using similar stimuli without pre-pulse to determine the percentage of the response inhibited. Data were analyzed using a three-way mixed ANOVA with stimulus intensity as a within-subject factor and the two injections as between-subjects factors. Because results revealed significant main effects of stimulus intensity on startle amplitudes and on pre-pulse inhibition, data from each stimulus were analyzed separately, using two-way ANOVA. Fisher's LSD comparisons were used to determine differences between dose groups of nicotine. Two subjects out of 90 were eliminated from the analysis because their startle response amplitudes were more than 2 standard deviations from their group mean. All tests were 2-tailed and used an alpha level of 0.05 or less to determine significance.

RESULTS

Table 2 presents PPI, in grams of weight change (as measured by the strain gauges inside the acoustic startle platforms as discussed in the methods section), using the 112 dB and the 122 dB stimuli. Results of the three-way mixed ANOVA revealed a significant main effect of stimulus intensity with greater startle amplitudes elicited by the 122 dB stimulus than by the 112 dB stimulus [$F(1,78)=18.07$, $p<.001$]. Subsequent two-way ANOVA revealed a significant main effect of injection 1 on pre-pulse inhibition when the 112 dB stimulus was presented [$F(2,78)=3.08$, $p<.05$]. The groups that received 0.5 mg/kg nicotine following hexamethonium treatment or mecamylamine following hexamethonium treatment had greater PPI than did the group that received only saline ($p<.05$). All groups, except that which received mecamylamine following hexamethonium treatment, were significantly different from the group that received 0.5 mg/kg nicotine following hexamethonium treatment ($p<.05$).

Figure 1 presents startle amplitudes to the 112 dB stimuli presented without pre-pulse (Figure 2a) and percentage of the startle response inhibited by the pre-pulse tone (Figure 2b). Presenting PPI as a percent helps to minimize the extent to which the magnitude of the ASR contributes to the amount of inhibition measured following the pre-pulse tone. Two-way ANOVA revealed a significant

interaction of injection 1 and injection 2 on the percentage of PPI when the 112 dB stimulus was used [$F_{(4,78)}=2.489$, $p<.05$]. This result indicates that nicotine and the nicotinic antagonists each played a role to affect PPI. Animals that had received saline alone had a smaller percent inhibition than did animals that received hexamethonium alone, with either dose of nicotine, or with mecamylamine ($p<.05$). Animals that received saline alone also had less inhibition than did animals that received 0.01 mg/kg nicotine with saline ($p<.05$). For nicotine alone, analyses revealed a significant effect of drug [$F_{(2,22)}=3.34$, $p<.05$] with 0.01 mg/kg nicotine enhancing PPI when compared with controls ($p<.05$). There were no significant effects of injection 1 or injection 2 on the amplitude of the acoustic startle response without pre-pulse.

Figure 2 presents startle amplitude to the 122 dB stimuli presented without pre-pulse (Figure 3a) and percent of the startle response inhibited by the pre-pulse tone (Figure 3b). Two-way ANOVA revealed a significant interaction of injection 1 and injection 2 on the percentage of PPI when the 122 dB stimulus was used [$F_{(4,78)}=2.613$, $p<.05$]. This result indicates that nicotine and the nicotinic antagonists each played a role to affect PPI. Animals that received saline alone had a smaller percent pre-pulse inhibition than did those that received hexamethonium with saline, hexamethonium with either dose of

nicotine, or hexamethonium with mecamylamine (p<.05).
Animals that received saline alone also had less inhibition
than did those that received 0.01 mg/kg nicotine with
saline. For nicotine alone, analyses revealed a significant
effect of drug [F(2,22)=4.36, p<.05] with either dose of
nicotine enhancing PPI when compared with controls (p<.05).
Mecamylamine with saline [F(1,15)=6.82, p<.05] and
hexamethonium with saline [F(1,15)=5.25, p<.05] also
enhanced PPI when compared with controls (p<.05). There
were no significant effects of injection 1 or injection 2 on
the amplitude of the acoustic startle response without pre-
pulse[1].

DISCUSSION

The present experiment examined effects of nicotine and
nicotinic-cholinergic antagonists on pre-pulse inhibition, a
measure thought to reflect processes that underlie attention
(Swerdlow, et al., 1986; Grunberg, et al., 1994). Central
or peripheral nicotinic antagonists were administered to
female rats prior to nicotine administration and PPI was
tested. The hypothesis that subjects would exhibit greater
startle response amplitudes in response to the 122 dB
stimuli than in response to the 112 dB stimuli was
supported. Subjects had significantly greater startle

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[1]It is relevant to note that the responses of animals in the
saline-saline group were comparable to those of the other groups
on day 2.

amplitudes when the 122 dB stimulus was presented than when the 112 dB stimulus was presented.

The hypothesis that acute administration of 0.01 mg/kg nicotine would increase ASR and PPI relative to controls was partially confirmed. Specifically, 0.01 mg/kg nicotine increased PPI but did not increase ASR relative to controls. These effects of nicotine on PPI are consistent with previous reports of an inverted U-shaped dose-effect of nicotine on pre-pulse inhibition (Acri, et al., 1994). These effects of nicotine also are consistent with the report of Curzon, et al. (1994).

The hypothesis that acute administration of 0.5 mg/kg nicotine would produce levels of ASR and PPI that are indistinguishable from controls also was partially confirmed. When the 112 dB stimulus was used, subjects that received 0.5 mg/kg nicotine with saline had levels of ASR and PPI that were indistinguishable from controls. This result is consistent with previous reports (Acri, et al., 1994) and may be consistent with an inverted U-shaped dose-effect of nicotine. When the 122 dB stimulus was used, however, subjects that received 0.5 mg/kg nicotine with saline had greater PPI than did subjects that received saline alone.

The hypothesis that acute administration of mecamylamine would result in a leftward shift in the dose-effect of nicotine, thereby rendering effects of 0.01 mg/kg

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nicotine that are indistinguishable from controls, also was
partially confirmed. Mecamylamine reduced the enhancing
effect of 0.01 mg/kg nicotine on percent PPI by 48% when the
112 dB stimulus was used (though the saline-0.01 mg/kg
nicotine group still differed from control) and by 30% when
the 122 dB stimulus was used. These reductions in effects
of 0.01 mg/kg nicotine when the 122 dB stimulus was used
resulted in effects of 0.01 mg/kg nicotine that were
indistinguishable from saline-saline controls. Results that
mecamylamine can inhibit nicotine's effects on PPI are
consistent with reports that mecamylamine can alter
nicotine-induced responses (Faiman, et al., 1992) and with
the suggestion that nicotine-induced changes in PPI are
mediated through a central cholinergic mechanism.

The hypothesis that acute injection of mecamylamine
would result in a leftward shift in the dose-effect of
nicotine, thereby rendering effects of 0.5 mg/kg nicotine
similar to the effects of 0.01 mg/kg nicotine, was partially
confirmed. Among subjects that were pretreated with
mecamylamine, 0.5 mg/kg nicotine produced levels of PPI that
were significantly greater than controls (and not
significantly different from levels of PPI produced by 0.01
mg/kg nicotine. Although results obtained using only 2
doses of nicotine can not unequivocally establish a shift in
dose-response, the fact that pretreatment with mecamylamine
can cause a high dose of nicotine to have effects that

resembled effects of a lower dose of nicotine are consistent with the hypothesis that pretreatment with mecamylamine would shift nicotine's dose-response curve to the left.

The hypothesis that pretreatment with hexamethonium would not alter effects of nicotine was partially confirmed. When the 112 dB stimulus was used, there were no significant effects of hexamethonium to alter effects of 0.01 mg/kg nicotine but, when the 122 dB stimulus was used, hexamethonium pretreatment altered levels of PPI produced by 0.5 mg/kg nicotine in a way that is consistent with a leftward shift in nicotine's dose-effect curve. More specifically, hexamethonium pretreatment rendered effects of 0.5 mg/kg nicotine that were similar to those produced by 0.01 mg/kg nicotine administered with saline. These effects of hexamethonium to alter PPI suggest that peripheral, as well as central, mechanisms affect PPI.

Finally, the hypothesis that neither mecamylamine nor hexamethonium would alter ASR or PPI in the absence of nicotine was partially confirmed. Neither antagonist altered ASR in the absence of nicotine, but both antagonists increased percent PPI when the 122 dB stimulus was used and hexamethonium additionally increased PPI when the 112 dB stimulus was used.

This finding, that mecamylamine and hexamethonium can alter PPI in a manner that is similar to that of nicotine suggests that nicotine and these nicotinic-cholinergic

antagonists may have similar mechanisms of action to affect PPI. If this interpretation is correct, then it is possible that mecamylamine, hexamethonium, and nicotine each influence PPI by inhibiting nicotinic receptors. In the case of the nicotinic antagonists, this inhibition may result from antagonism of nicotinic receptors. In the case of nicotine, the proposed inhibition may result from desensitization of nicotinic receptors. Marks, et al. (1983) cited receptor desensitization as an explanation for the paradoxical up-regulation of nicotinic cholinergic receptors following chronic agonist treatment (Marks, Burch, & Collins, 1983). Sharp and Beyer (1986) reported that a single (IP) injection of nicotine (0.5 mg/kg) can produce desensitization to the stimulatory effects of nicotine on adrenocorticotropic hormone (ACTH) and prolactin secretion. Acute nicotine pretreatment also has been reported to desensitize nicotine-induced dopamine release (Grady, Marks, & Collins, 1994), nicotine-induced norepinephrine release (Sharp & Matta 1993), and nicotine-induced activation of c-fos mRNA (Sharp, Beyer, McAllen, Hart, & Matta, 1993). Behaviorally, receptor desensitization has been offered to explain disruptions in nicotine discrimination in rats following a bolus injection of nicotine (0.8 mg/kg, IP) (James, Villanueva, Johnson, Arezo, & Rosecrans, 1994) and to explain acute and chronic tolerance effects to nicotine (Rosecrans & Karan 1993; Balfour, 1994). Results of the

current experiment suggest that receptor desensitization also may play a role in nicotine's effects on sensory gating.

It is important to note that some of the present results differ from those reported by Curzon et al. (1994) who reported no effect of a low dose of mecamylamine (5 μm/kg) on PPI and reductions in PPI following a higher dose of mecamylamine (50 μm/kg). One possible explanation for these different results is the fact that Curzon et al. (1994) used 225 g male Long-Evans rats, whereas the present experiment used 250 g female Sprague-Dawley rats. Reports reveal marked age (Acri, Brown, Saah, & Grunberg, 1995) and strain (Acri, et al., 1995; Glowa & Hansen 1994) differences in pre-pulse inhibition and in responses to nicotine. Specifically, Long-Evans rats (as used by Curzon, et al., 1994) are significantly less responsive to acoustic startle stimuli and are less sensitive to the inhibitory effects of pre-pulse than are Sprague-Dawley rats (as used in the present experiment). Additionally, young rats (as used by Curzon, et al., 1994) are less sensitive to nicotine's enhancement of PPI than are older rats (as used in the present experiment). Further evidence indicates that male rats (as used by Curzon, et al., 1994) are less sensitive to many effects of nicotine than are female rats (as used in the present experiment) (Grunberg, Winders, & Wewers, 1986; Winders & Grunberg 1989). Though these important strain,

age, and sex differences may have contributed to the differences between present results and those of Curzon, et al. (1994), additional data are necessary to fully understand effects of nicotine and nicotinic antagonists on pre-pulse inhibition.

Of additional interest is the possibility that effects of nicotine and/or nicotinic antagonists on ASR or PPI may have been influenced by the intensity of the startle stimulus used. Eyesenk (1973) suggested that nicotine can have different effects in different individuals depending on their initial level of arousal. More specifically, Eyesenk (1973) suggested that individuals with low levels of initial arousal will experience stimulation by nicotine whereas individuals with high levels of initial arousal will experience tranquilization by nicotine. Acri (1994) reported differential effects of nicotine and stress on ASR and PPI when administered with and without restraint stress. Specifically, chronic infusion of 6 mg/kg/day nicotine did not affect ASR or PPI when administered alone but enhanced ASR and PPI when administered with arousal produced by restraint stress. 12 mg/kg/day nicotine enhanced ASR and PPI when administered alone but had no effect on ASR or PPI when administered with arousal produced by restraint stress. This finding was interpreted as a shift in nicotine's dose-effect on ASR and PPI by stress and has been offered as an explanation of why some smokers smoke

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more under stress (Acri 1994). To the extent that the high decibel stimulus used presently (122 dB) produced high levels of arousal and the low decibel stimulus produced low levels of arousal, one may expect differential effects of nicotine or nicotinic antagonists depending on which stimulus intensity is used. However, there were no statistically significant interactions of stimulus intensity with any of the other independent variables nor was there any meaningful difference between the pattern of effects observed using the 112 dB stimulus and the pattern of effects observed using the 122 dB stimulus. Therefore, it can be concluded that arousal was not a significant factor contributing to the presently effects of nicotine and nicotine antagonists on ASR and on PPI.

Finally, it should be noted that most rats emit ultrasounds when startled by an acoustic or tactile stimulus and that these ultrasounds may influence the startle responses of other subjects (Kaltwasser, 1990; Miczek, Vivian, Tornatzky, Farrell, & Sapperstein, 1992). In the present experiment rats were tested in groups of four. Therefore, it is possible that rats tested concurrently may have been influenced each other's responses. To minimize this potential confound, several drug treatment groups were represented in every group that were run concurrently.

In summary, the present results suggest that nicotine can enhance PPI, perhaps through its effects on attention

and sensory gating processes. This finding is consistent with previous reports that nicotine can enhance attentiveness in humans (Wesnes & Warburton, 1983; Wesnes, et al., 1983; Wesnes & Revell, 1984; Wesnes & Warburton, 1984; Provost & Woodward, 1991) and in rats (Acri, et al., 1991; Acri, et al., 1994; Acri, 1994). Similar enhancing effects were observed following hexamethonium or mecamylamine administration suggesting that nicotine and nicotinic antagonists may share a similar mechanism of action to affect sensory gating. Specifically, nicotinic antagonists may act through receptor antagonism, whereas nicotine may act through receptor desensitization to affect PPI.

An additional point of note is that nicotine, in the present experiment, had effects on PPI that are consistent with an inverted U-shaped dose-effect as previously described (Acri, et al., 1994). Specifically, a moderate dose of nicotine (0.01 mg/kg) increased PPI, whereas a higher dose (0.5 mg/kg) produced levels of PPI that were indistinguishable from controls. If receptor antagonism, achieved via receptor desensitization, underlies effects of nicotine to increase PPI, then it would be expected that a higher dose of nicotine (or an effective dose of nicotinic antagonists) would also increase PPI. The presence of a descending limb in nicotine's dose-effect implies that a different mechanism may underlie effects of a moderate dose of nicotine to increase PPI, and effects of a higher dose of

nicotine to inhibit PPI. Future experiments, using
additional doses of nicotine and several doses of nicotinic
antagonists, may help to clarify whether the inverted U-
shaped dose-effect of nicotine reflects a single, underlying
mechanism with different effects at different dosages, or
whether it reflects two different underlying mechanisms, one
that increases and one that decreases PPI. This information
may help to clarify effects of nicotine on attention and may
further our understanding of nicotine's potential as a
therapeutic pharmacologic agent.

TABLES

Table 1. Experimental design

2ND INJECTION

1ST INJECTION	saline	0.01 mg/kg nicotine	0.5 mg/kg nicotine
saline	N=9	N=9	N=9
1.0 mg/kg mecamylamine	N=9	N=9	N=9
1.0 mg/kg hexamethoniu	N=9	N=9	N=9

Table 2. Pre-pulse inhibition (PPI) presented as the reduction in the startle response occurring as a result of the pre-pulse tone. PPI was calculated as: [(startle response when the stimuli were presented without a pre-pulse) - (startle response when the the stimuli were presented with a pre-pulse)]. Means ± S.E.M.

PPI using 112 dB stimulus

2ND INJECTION

1ST INJECTION	saline	0.01 mg/kg	0.5 mg/kg	1.0 mg/kg mecamyalmine
saline	63 ± 9	107 ± 22 *	89 ± 18 *	
1.0 mg/kg mecamylamine	79 ± 1	90 ± 13 *	88 ± 15 *	
1.0 mg/kg hexamethonium	89 ± 1	101 ± 13 *	156 ± 23 #	122 ± 15 #

PPI using 122 dB stimulus

2ND INJECTION

1ST INJECTION	saline	0.01 mg/kg	0.5 mg/kg	1.0 mg/kg mecamyalmine
saline	107 ±	147 ± 26	135 ± 23	
1.0 mg/kg mecamylamine	119 ±	119 ± 14	142 ± 15	
1.0 mg/kg hexamethonium	139 ±	150 ± 20	188 ± 26	153 ± 17

* denotes groups significantly different from hexamethonium + 0.5 mg/kg nicotine.
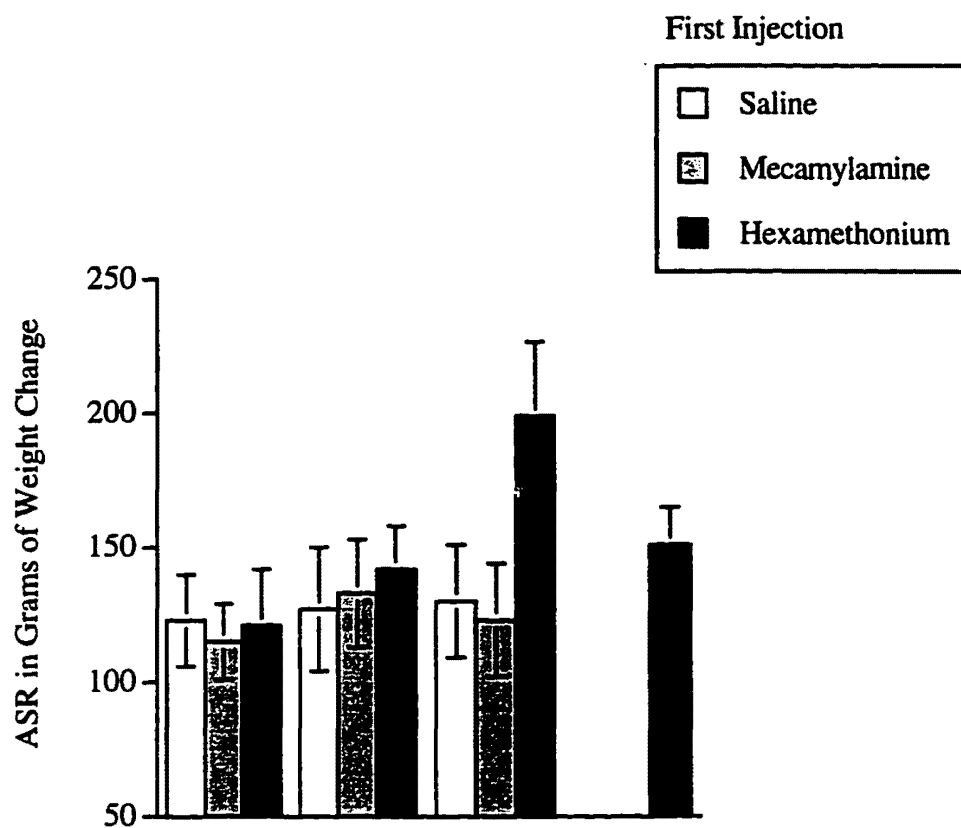#denotes groups significantly different from saline

FIGURES

Figure 1a

Figure 1b

First Injection
☐ Saline
▨ Mecamylamine
■ Hexamethonium

Figure 2a

First Injection

- ☐ Saline
- ▨ Mecamylamine
- ■ Hexamethonium

ASR in Grams of Weight Change

300

250

200

150

100

Figure 2b

% Pre-pulse Inhibition

90

80

70

60

50

Saline

0.01 mg/kg Nicotine

0.5 mg/kg Nicotine

Mecamylamine
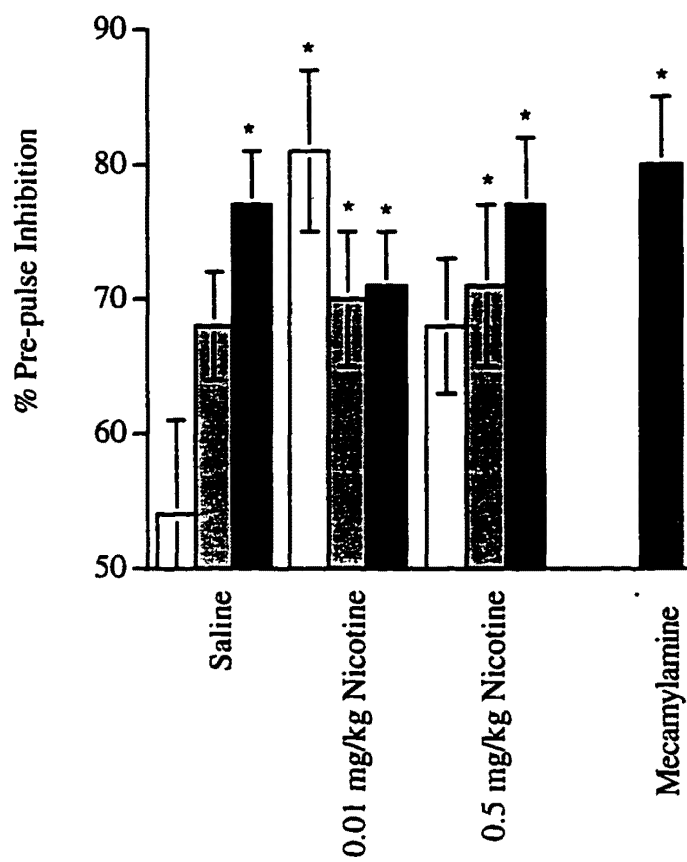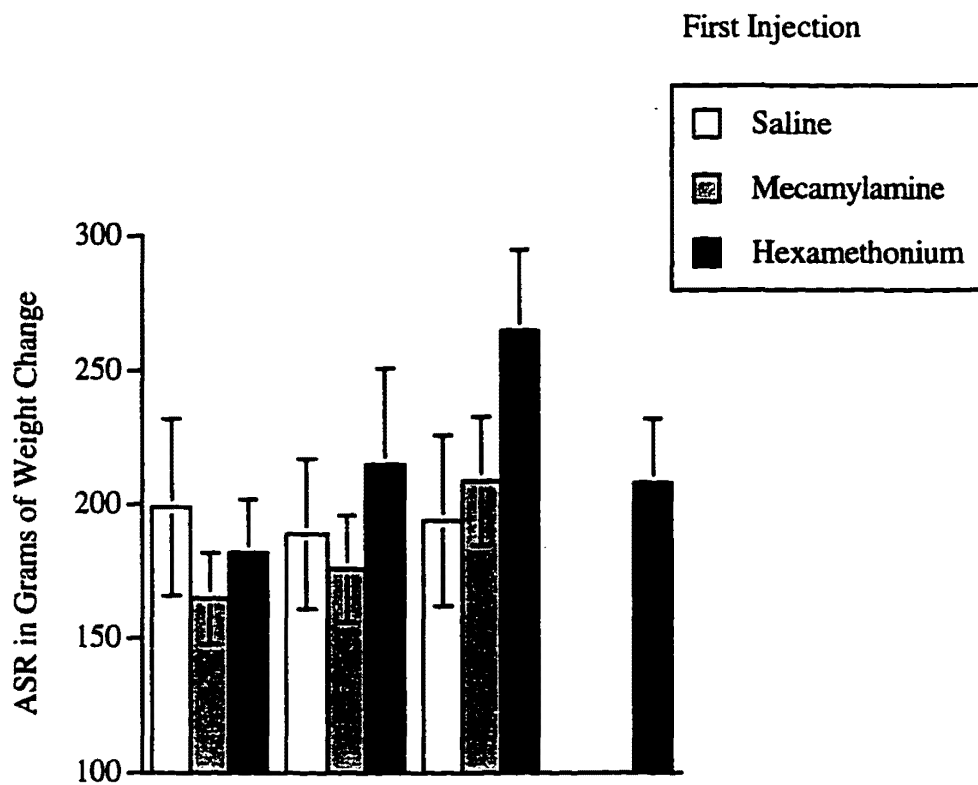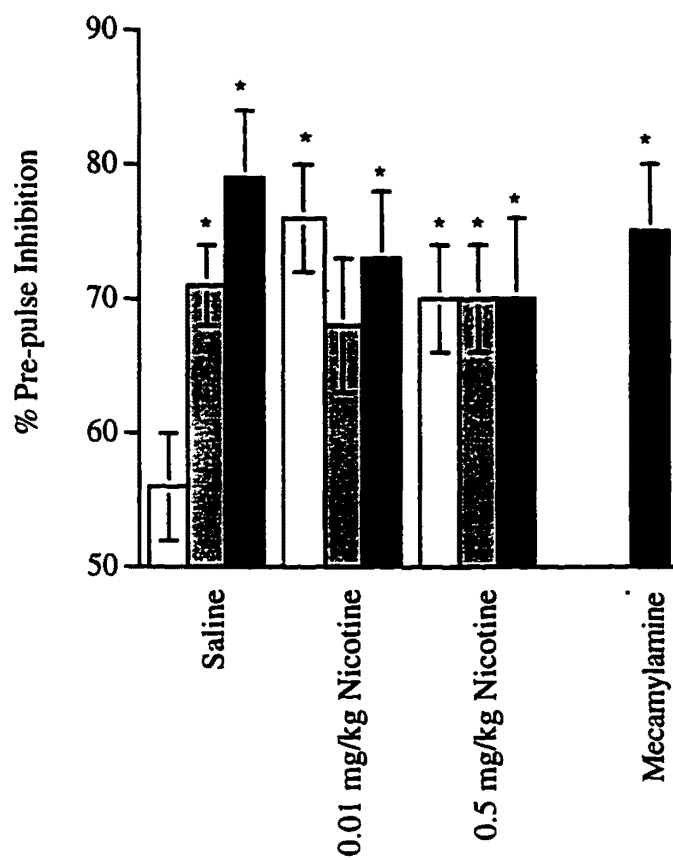
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